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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/517,784	12/13/2004	Gideon Gross	GROSS32	4624

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EXAMINER	
RAWLINGS, STEPHEN L	

ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/517,784	GROSS ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5,11,12,15,16,18,19,21,22,29-33,35,40,41,43,47,52,56 and 57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5,11,12,15,16,18,19,21,22,29-33,35,40,41,43,47,52,56 and 57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20100811*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed August 11, 2010, is acknowledged and has been entered. Claims 13, 14, 17, 20, 23-28, 34, 36-39, 42, 44, 48-51, and 53 have been canceled. Claims 1, 11, 12, 15, 16, 18, 19, 21, 32, 35, 43, 47, 56, and 57 have been amended.

2. Claims 1, 3, 5, 11, 12, 15, 16, 18, 19, 21, 22, 29-33, 35, 40, 41, 43, 47, 52, 56, and 57 are pending in the application and have been examined.

Information Disclosure Statement

3. The information disclosure filed August 11, 2010, has been considered in part. An initialed copy is enclosed.

Priority

4. Applicant's claim under 35 U.S.C. §§ 119(e) and/or 120, 121, or 365(c) for benefit of the earlier filing date of PCT/IL03/00501, filed June 12, 2003, which claims benefit of Provisional Application No. 60/388,273, filed June 12, 2002, is acknowledged.

However, claims 1, 3, 5, 11, 12, 15, 16, 18, 19, 21, 22, 29-33, 35, 40, 41, 43, 47, 52, 56, and 57 do not properly benefit under §§ 119 and/or 120 by the earlier filing dates of the priority documents claimed, since those claims are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure.

To receive benefit of the earlier filing date under §§ 119 and/or 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994). See M.P.E.P. § 201.11.

Then, apart from this issue, it is further noted that many of the claims do not properly benefit from the earlier filing date of Provisional Application No. 60/388,273 since that application fails to provide written support for the language of the claims. Without limitation, but as an example, it is noted that claim 1, for example, is drawn to a polynucleotide encoding a fusion polypeptide comprising the full or partial cytoplasmic domain of CD40; yet, it appears that the provisional application does not disclose such a fusion polypeptide and thus fails to provide written support for such a claim.

Accordingly, the effective filing date of the claims is deemed the filing date of international application PCT/IL03/00501, namely June 12, 2003.

Grounds of Objection and Rejection Withdrawn

5. The grounds of objection and rejection set forth in the previous Office action mailed March 11, 2010, have been withdrawn in favor of the new grounds of objection or rejection set forth below in this Office action.

Grounds of Objection and Rejection Maintained

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. The rejection of claims 1, 3, 5, 11, 12, 15, 16, 18, 19, 21, 22, 29-33, 35, 40, 41, 43, 47, 52, 56, and 57 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, is maintained. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

At pages 20-43 of the amendment filed August 11, 2010, Applicant has traversed the propriety of maintaining this ground of rejection, arguing in brief that the claimed

invention has a specific and substantial asserted utility since it can be used to prevent tumors in mice[1], there are commercially available products on the market, which are currently in clinical use for the treatment of cancer, and certain embodiments of the claimed invention have been used to prevent tumors in mice immunized before inoculation with tumor cells.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

M.P.E.P. § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

In this case, it is submitted that the skilled artisan could not use the claimed invention in any specific manner, as intended, to prevent or treat any one particular type of cancer or an infectious disease without undue and unreasonable experimentation;

[1] See, e.g., Applicant's remarks at page 25 of the amendment filed August 11, 2010.

and if there is an embodiment of the claimed invention that could be used in the manner intended without need to perform undue and unreasonable experimentation, it is not immediately which embodiment that is, as there are so very many too inadequately described to recognize without the need to first complete the inventive process to discover which ones those are.

Applicant is duly reminded that reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

Thus, the overly broad scope of the claims would merely serve as an invitation to one skilled in the art to identify a polynucleotide according to the claims, which comprises at least one tumor-associated antigenic peptide comprising an MHC class I epitope having the ability to elicit a prophylactically and/or therapeutically effective anti-tumor immune response in a subject; yet, defining a substance by its principal biological activity amounts to an alleged conception having no more specificity than that of a wish to know the identity of any material with that biological property. See *Colbert v. Lofdahl*, 21 USPQ2d 1068, 1071 (BPAI 1991).

In this instance, it is apparent that the amount of guidance, direction, and exemplification disclosed in the specification is not reasonably commensurate in scope with the claims; and in fact, it is duly noted that there are no disclosures in this application pertaining to any exemplifying experiments or studies to show that the claimed inventions can be used as intended to prevent or treat cancer or infectious disease.

Therefore, in light of the publications cited in the preceding Office action in support of this position – and indeed there is now a preponderance of factual evidence of record showing that cancer vaccines are ineffective, *even if antigen-specific T-lymphocytes can be activated by immunization protocols* – it is submitted that specification should only be regarded as, at best, only reasonably adequate to enable the skilled artisan to *make* the claimed products, but not to use those products, as intended to prevent or treat cancer or infectious disease, without undue and unreasonable experimentation.

Here, because the art is so highly unpredictable, in the absence of an amount of guidance, direction, and exemplification that is reasonably commensurate in scope with the claims, the skilled artisan would not accept the assertion that the claimed invention can be used to prevent or treat any given type of cancer or infectious disease. Consequently, if a patent were to issue upon this application, given only the disclosure therein, one skilled in the art could not use the claimed invention as is intended to prevent or treat cancer or infectious disease without first having to determine the identify of the one or more tumor-associated antigenic peptides comprising an MHC class I epitope having the ability to elicit a prophylactically and/or therapeutically effective anti-tumor immune response in a subject. As such, a patent granted upon this application could only be viewed as a mere invitation to the skilled artisan to elaborate upon the disclosure so as to determine how the claimed invention can be used to prevent or treat cancer or infectious disease, or to finish the inventive process. Such need to finish the inventive process would constitute a requirement that the practitioner perform an undue amount of experimentation.

At page 26 of the amendment filed August 11, 2010, Applicant has argued that this ground of rejection should not be maintained because there are some products on the market that are currently being used in the clinical setting to treat cancer. In particular Applicant has remarked that Provenge™ (sipuleucel-T) is used to stimulate a

T-cell-mediated immune response in advanced prostate cancer patients[2], but in response, it is aptly noted that the claims are not directed to this particular product or a method of using this particular product for the treatment of advance prostate cancer in human patients. Instead the claims are directed to a polynucleotide encoding a fusion polypeptide comprising a tumor-associated antigen comprising an MHC class I epitope and although the specification describes a number of different tumor-associated antigens, including prostatic acid phosphatase (PAP), it does not appear to teach or suggest the use of the antigen peptide of which Provenge™ is comprised. Then, as explained in the preceding Office action, the specification teaches that the claimed invention can be used to treat any of a plurality of etiologically and pathologically disparate types of cancer and infectious diseases, but fails to provide guidance as to which particular embodiments of the claimed invention might be used to treat which diseases; and moreover the specification fails to exemplify the use of the claimed invention to treat prostate cancer, for example, and discloses no factual evidence that any of the embodiments encompassed by the claims can be used effectively to treat any other disease. So, while perhaps a product, such as Provenge™ may be used effectively to improve the overall survival of prostate cancer patients, there is no

[2] Brower (*J. Natl. Cancer Inst.* 2010 Aug 4; **102** (15): 1108-1110) discloses that in a recent phase III clinical trial, known as IMPACT, patients taking Provenge™ had a 4-month median improvement in overall survival and although 4 months is a modest increase, it has been reported that some clinicians view the FDA's approval of this product as "a milestone for the entire class of immunotherapeutic cancer vaccines" – nonetheless, Brower further discloses that despite the promise of the results of the trial, just how Provenge™ works is one of many unanswered questions about treatment vaccines and it is apparent that the best way to measure progression after treatment with immunotherapies is still not clear, such that questions remain about the direct and indirect effects of immune therapies on cancer cells and their microenvironments, at what stage of disease vaccines should be used, and how they can best be combined with other treatments. As such, it is apparent that even today the instant disclosure should not be regarded as reasonably enabling of the use of the broadly claimed products; but more apparent, it would not have been enabling as of the effective filing date of this application, so as to be sufficient to satisfy the enablement requirement set forth under 35 U.S.C. § 112, first paragraph. Then, too, it is aptly noted that despite some clinician's reaction to the published results of the clinical trial, others are calling for more careful scrutiny of the data and more caution in concluding that the agent can be used therapeutically: Madan et al. (*Oncologist.* 2010; **15** (9): 969-975), for example, comments that the findings of the clinical trial "have been met with skepticism, primarily because the agent did not change initial disease progression and yet led to longer survival" (abstract). As a consequence, Madan et al. urges that clinicians need to reconsider how they measure success, since several agents have been approved that produce superior disease progression results, but do not affect overall survival; and then also, given the toxicity and costs of cancer therapies, perhaps studies should put more weight on long-term survival endpoints than on short-term endpoints that may be less consequential (see entire document, e.g., the abstract).

evidence in the specification that the claimed invention might also be used to achieve such clinical benefit.

Then, beginning at page 38 of the amendment filed August 11, 2010, it is noted that Applicant has argued that the declaration by Dr. Gross shows that the claimed invention, when used as a vaccine administered before inoculation of mice with tumor cells, is effectively used to protect mice from tumors. In response, it is first noted that the evidence presented is not commensurate in scope with the claimed subject matter and as such it is submitted that the evidence should not be considered reasonably representative of the results that might be achieved in practicing the claimed invention. Then, in further response, many similar studies in mice have been performed, some of which are described in the publications that have been cited in the prior Office action to support of the Office's position herein, and despite any initial promise, the successful use of cancer vaccines, in general, in preventing and treating humans has remained elusive.

To further address this point, it is noted that Gura (of record), for example, addresses the common lack of extrapolation of the results of studies performed *in vivo* using mouse models to accurately and reliably predict the effects of the same treatments of human patients.

More recently, Dennis (*Nature*. 2006 Aug 7; **442**: 739-741) reports, despite their present indispensableness, mouse models, such as xenografts, have only limited utility in predicting the clinical effectiveness of anticancer treatments; see entire document (e.g., page 739, column 2). Dennis explains there is a "laundry list" of problems associated with the use of mice to model human diseases, such as cancer (page 739, column 1). Accordingly, Dennis reports, "[a]lthough virtually every successful cancer drug on the market will have undergone xenograft testing, many more that show positive results in mice have had little or no effect on humans, possibly because the human tumours are growing in a foreign environment" (page 740, column 1). Therefore, quoting Howard Fine, Dennis concludes: " 'Mice are valuable but they are, after all, still mice' ", suggesting the best study subject will always be the human (page 741, column 3).

As a consequence of poor extrapolation, both Gura and Dennis teach that studies using mouse models often lead development of good mouse drugs rather than good human drugs, which suggests the need for careful evaluation of the effects of therapeutic agents in humans before transitioning from preclinical studies to clinical application.

Not inconsistently, Schuh (*Toxicologic Pathology*. 2004; **32** (Suppl. 1): 53-66) reviews the trials, tribulations and trends in tumor modeling in mice to disclose, for example, that "[c]ommon reliance on survival and tumor burden data in a single mouse model often skews expectations towards high remission and cure results; a finding seldom duplicated in clinical trials" (abstract). Furthermore, Schuh discloses, "[d]espite historical significance and ongoing utility, tumor models in mice used for preclinical therapeutic intervention often error towards false positive results and curing cancer in mice" (page 62, column 1). Given the noted limitations of xenograft models, Schuh suggests that testing in tumor-bearing animals may help to improve the predictive value of animal modeling; see entire document (e.g., the abstract).

Bibby (*Eur. J. Cancer.* 2004 Apr; **40** (6): 852-857) teaches that in the interest of finding more clinically relevant models, orthotopic models have been developed; see entire document (e.g., the abstract). In such "orthotopic" models, treatment is initiated after removal of the primary tumor and distant metastases are well established and macroscopic. These models have their advantages, but the procedures involved in using such models are far more difficult and time-consuming than conventional subcutaneous (e.g., xenograft) models; see, e.g., page 855, column 2.

The position of the Office is further substantiated by the teachings of Peterson et al. (*Eur. J. Cancer.* 2004; **40**: 837-844). Peterson et al. teaches numerous agents have show exciting activity in preclinical models and yet have had minimal activity clinically; see, e.g., the abstract. Such disappointments, Peterson et al. discloses, "have led to reasonable skeptism about the true value of both syngeneic and xenograft rodent tumour models in accurately identifying agents that will have important clinical utility" (abstract). Peterson et al. reviews the limitations of the xenograft models; see entire document (e.g., page 840, column 2).

So then it seems apparent that the problem with accepting an assertion that the claimed invention can be used to effectively prevent or treat cancer and infectious diseases lies in the fact that the data generated using such mouse models cannot be reasonably extrapolated to reliably and accurately predict whether the claimed invention can be used to attenuate at least a substantial number of pathoangiogenic conditions comprising cancer and furthermore, as of yet, the clinical, therapeutic application of cancer vaccines to attenuate cancer has been met with very little success. Again, there are many references cited in preceding Office actions, which describe such disappointing results and attribute the lack of success to various differences, such as the poor extrapolation of promising preclinical data to predict clinical efficacy; Wang et al. (or record), for example, reviews the state of the art of T-cell-directed cancer vaccines for treatment of melanoma and states:

> Saved for scattered reports, however, the success of these approaches has been limited and T-cell-directed vaccination against cancer remains at a paradoxical standstill whereby anticancer immunisation can be induced but is not sufficient, in most cases, to induce tumour regression (abstract).

Wang et al. further states:

> Among the questions raised by this paradoxical observation [that systemic T-cell responses to vaccines often do not lead to objective clinical tumor regression] stands the enigma of whether tumour resistance to immunotherapy is due to insufficient immune response or because tumour cells rapidly adapt to immune pressure by switching into less immunogenic phenotypes [citations omitted].

In addition, Kelland (*Eur. J. Cancer.* 2004 Apr; **40** (6): 827-836) has reviewed the reliability of the model in predicting clinical response; see entire document (e.g., the abstract). While the successful use of such models in cytotoxic drug development is conclusive, Kelland discloses that today there is far less focus on the development of such drugs (page 833, column 2); rather, the focus is upon the development of "molecularly-targeted", largely cytostatic drugs, such as those disclosed in the instant application, which may act in synergy with other drugs to selectively reduce or inhibit the growth of neoplastic cells (e.g., page 885). In particular, where such drugs are naked humanized antibodies that act through mechanisms such as ADCC, Kelland states the

models are of limited value, because such mechanisms depend upon the recruitment of the host's (i.e., mouse) immune response, which differs from or is not reflective of that found in man (page 834, column 2). With such limitations of the xenograft model in mind, Kelland suggests that the case for using the model within a target-driven drug development cascade need to be justified on a case-by-case basis (page 835, column 1). Still, Kelland et al. does not altogether discount the usefulness of such models, since, at present, "it is premature and too much a 'leap of faith' to jump directly from *in vitro* activity testing (or even in silico methods) to Phase I clinical trials (via preclinical regulatory toxicology)" (page 835, column 2). Kelland, however, does not advocate the use of a single xenograft model to exhort one to accept assertions of the effectiveness of treating multiple and different diseases using the same agent, as has been done in the instant application, since Kelland compels one to decide on a case-by-case basis whether such a model is suitable or not.

So again, Gura (of record) teaches that although researchers had hoped that xenografts would prove to better models for studying cancer in humans and screening candidate therapeutic agents for use in treating patient diagnosed with cancer, "the results of xenograft screening turned out to be not much better than those obtained with the original models". Gura states that as a result of their efforts, " '[w]e had basically discovered compounds that were good mouse drugs rather than good human drugs' ".

With further regard to the predictive value of various different preclinical models, Voskoglou-Nomikos et al. (*Clin. Cancer Res.* 2003 Sep 15; 9: 4227-4239) reports in a retrospective analysis that mouse allograft models were not predictive and xenograft models were only predictive for non-small cell lung and ovarian cancers, but not for breast or colon cancers; see entire document (e.g., the abstract).

Finally, Saijo et al. (*Cancer Sci.* 2004 Oct; **95** (10): 772-776) recently reviewed the reasons for negative phase III trial of molecular-target-based drugs and their combinations; see entire document (e.g., the abstract). Saijo et al. discloses that while numerous phase III trials have been conducted upon the basis of promising preclinical data such as that disclosed in the instant application, few have yielded strongly positive results, and the majority of results have been negative (e.g., abstract). Saijo et al.

discloses that there are problems in preclinical prediction of combined effects of anticancer drugs, and the results of preclinical prediction of combined effects have been very poor (page 773, column 2). Saijo et al. teaches many reasons for the poor predictability of combined effects (page 774, Table 6).

Thus, taken collectively, there is a preponderance of factual evidence of record that the showing provided in the supporting disclosure would not enable the skilled artisan to practice the claimed invention without undue experimentation, as required under the provisions of 35 U.S.C. § 112, first paragraph.

In conclusion, then, although Applicant's arguments have been carefully considered, upon equally careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), it has been determined that the amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not have been sufficient to have enabled the skilled artisan to make and/or use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. The rejection of claims 1, 3, 5, 11, 12, 15, 16, 18, 19, 21, 22, 29-33, 35, 40, 41, 43, 47, 52, 56, and 57 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is maintained.

Beginning at page 43 of the amendment filed August 11, 2010, Applicant has traversed the propriety of maintaining these grounds of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

As before noted, in accordance with a recent decision by the Federal Circuit (*Halliburton Energy Services Inc. v. M-I LLC*, 85 USPQ2d 1654, 1658 (Fed. Cir. 2008)):

> 35 U.S.C. § 112, ¶ 2 requires that the specification of a patent "conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." Because claims delineate the patentee's right to exclude, the patent statute requires that the scope of the claims be sufficiently definite to inform the public of the bounds of the protected invention, i.e., what subject matter is covered by the exclusive rights of the patent. Otherwise, competitors cannot avoid infringement, defeating the public notice function of patent claims. Athletic Alternatives, Inc. v. Prince Mfg., Inc., 73 F.3d 1573, 1581 (Fed. Cir. 1996) ("[T]he primary purpose of the requirement is 'to guard against unreasonable advantages to the patentee and disadvantages to others arising from uncertainty as to their [respective] rights.'") (quoting Gen. Elec. Co. v. Wabash Appliance Corp., 304 U.S. 364, 369, (1938)). The Supreme Court has stated that "[t]he statutory requirement of particularity and distinctness in claims is met only when [the claims] clearly distinguish what is claimed from what went before in the art and clearly circumscribe what is foreclosed from future enterprise." United Carbon Co. v. Binney & Smith Co., 317 U.S. 228, 236 (1942).

Claims 1, 3, 5, 11, 12, 15, 16, 18, 19, 21, 22, 29-33, 35, 40, 41, 43, 47, 52, 56, and 57 are indefinite for the following reasons, thereby failing to satisfy the requirements set forth under 35 U.S.C. § 112, second paragraph:

(a) Claim 1, for example, is directed to a polypeptide that is capable of "high level presentation of antigenic peptides on antigen-presenting cells"; yet, it cannot be ascertained relative to what standard of comparison a determination of the level of presentation of antigenic peptides by the APCs must be made, so as to know whether or not the level is considered "high".

This is apparently important since it is presumed that not all polypeptides are capable of "high level presentation of antigenic peptides on antigen-presenting cells"; and since the claims are directed to only those that are, it is imperative that the artisan be reasonably apprised as to the identities of those that are or otherwise have means for determining which polypeptides are encompassed by the claims, and which are not.

Even so, it also cannot be ascertained under what relative conditions the polypeptide must be *capable of* such high level presentation, if not always. When and why are the claimed polypeptides said to have such capability, especially when it would seem that the presentation of antigenic peptides is a function of the cell and not the polypeptide?

For these reasons, it is submitted that the claims are too vague and fail to delineate claimed subject matter with the requisite clarity and particularity to permit the skilled artisan to know or determine infringing subject matter, so as to satisfy the requirements set forth under 35 U.S.C. § 112, second paragraph.

Applicant has responded to the preceding Office action arguing to the contrary that the claims are indefinite for this reason because the specification "clearly discloses the meaning of 'high level presentation of antigen peptide on antigen-presenting cells', but then comments that the meaning must be surmised from the examples and that it is based upon the measurement of three different parameters. In response to this argument it is again submitted that the degree to which the level of presentation of antigenic peptides on antigen-presenting cells must be "high" cannot be ascertained, even given the examples disclosed in the specification. Moreover, despite the examples which describe the levels at which *certain* polypeptides are presented by antigen-presenting cells expressing those polypeptides, it still cannot be ascertained relative to what standard of comparison a determination of the level of presentation of antigenic peptides by the APCs must be made, so as to know whether or not the level is considered “high”. Besides, Applicant is duly reminded that although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Here, too, it appears that Applicant is basing their arguments on features of the disclosed invention, which are not claimed, since the claims do not make any reference to the three different parameters to which Applicant has referred in addressing this rejection. Again, it is imperative that the artisan be reasonably apprised as to the identities of the polypeptides that capable of "high' level expression on antigen-presenting cells or otherwise have means for determining which polypeptides are encompassed by the claims, and which are not.

(b) The claims are indefinite because the claims use of the designations such as “CD40’, “MAGE” and “gp100” as the sole means of identifying the polypeptides or antigens to which the claims refer. The use of laboratory designations only to identify a particular polypeptide or a family of polypeptides renders the claims indefinite because

different laboratories may use the same laboratory designations to define completely distinct polypeptides.

For example, the terms "MAGE" and "BAGE" do not identify a single particular polypeptide but rather a family of structurally and functionally disparate family members.

Although some members of a given family may be associated with cancer (e.g., are overexpressed by cancer cells relative to normal cells of the corresponding tissue or organ), other members are not.

De Plaen et al. (of record), for example, reviews the structure, chromosomal localization and expression of twelve genes encoding members of the MAGE family of proteins; see entire document (e.g., the abstract). De Plaen et al. teaches six of the members of the gene family were found to be expressed at a high level in a number of tumors of various histological types; while five were very weakly expressed in all samples tested, and one, namely MAGE 7, was not transcribed at all in the ninety-five tumor samples tested (page 367, column 1).

Just as not all members of the MAGE family of proteins are associated with cancer, particularly, since is it not obvious what, if any, association the weakly expressed MAGE proteins have, it is apparent that the use of the term "MAGE" alone to identify the antigens that are regarded as part of the invention should not be considered sufficient to delineate the subject matter with the requisite clarity and particularity to satisfy the requirements set forth under 35 U.S.C. § 112, second paragraph. The same is true of any other such terms, which identify not particular polypeptides but rather any of a plurality of structurally and/or functionally disparate polypeptides, even if they are related as members of a given family.

Thus, it is apparent that the same term is often used in the art to describe not one polypeptide, but rather a plurality of polypeptides, which might be structurally and/or functionally related, but otherwise distinct. As another example, it is noted that the same terms are often used to describe various isoforms that are encoded by a single gene, which result from translation of alternatively spliced transcripts of that gene; as another example, the same terms are frequently used to identify polypeptides that occur in different species of animals, which although sharing certain structural and/or

functional characteristics have distinct structures and/or functions (e.g., orthologs and paralogs).

The term "CD40", for example, identifies not just one particular polypeptide, but rather any of a number of orthologs encoded by genes in different mammals.

The same is true of the term "human CD3 ζ polypeptide", which has been described as having a number of structurally and functionally disparate isoforms. Tsuzaka et al. (of record), for example, describes mRNA slice variants encoding variant forms of the polypeptide that have been observed in the peripheral blood T cells from systemic lupus erythematosus patients; see entire document (e.g., the abstract). Not dissimilarly Atkinson et al. (of record) also describes isoforms of human CD3 polypeptide encoded by an alternatively spliced mRNA in T cells or natural killer cells, which have altered signal transducing activities as compared to other isoforms; see entire document (e.g., the abstract).

35 U.S.C. § 112, second paragraph, requires the claim define the metes and bounds of the subject matter that is regarded as the invention with such clarity and particularity to permit the skilled artisan to know or determine infringing subject matter; because the terms used to describe the polypeptides to which the claims are directed do not unambiguously identify those polypeptides, this requirement has not been met.

It is suggested that this issue might be remedied by amending the claims to include a recitation of the amino acid sequence of the polypeptides by reference to one or more specific sequence identification numbers of amino acid sequences set forth in the Sequence Listing because the amino acid sequence of a polypeptide is a unique identifier that unambiguously defines a given polypeptide.

Beginning at page 48 of the amendment filed August 11, 2010, Applicant has argued to the contrary that the use of such nomenclature alone to identify the particular polypeptides to which the claims are directed does not render the claims indefinite because the skilled artisan would not consider using peptides derived from isoforms or family members that are associated with cancer since it would not serve his purpose. In response, the question is not whether a skilled artisan would use peptides derived from polypeptides that would not serve his purpose as much as what are the metes and

bounds of the subject matter that is regarded as the invention by Applicant and do the claims clearly and particularly delineate those metes and bounds such that the skilled artisan would know or could determine infringing subject matter.

In determining whether the claims satisfy the requirement set forth under § 112, second paragraph, M.P.E.P. § 2106 (II) states:

> USPTO personnel are to give claims their broadest reasonable interpretation in light of the supporting disclosure. *In re Morris*, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997). **Limitations appearing in the specification but not recited in the claim should not be read into the claim**. *E-Pass Techs., Inc. v. 3Com Corp.*, 343 F.3d 1364, 1369, 67 USPQ2d 1947, 1950 (Fed. Cir. 2003) (claims must be interpreted "in view of the specification" **without importing limitations from the specification into the claims unnecessarily**). *In re Prater*, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550- 551 (CCPA 1969). See also *In re Zletz*, 893 F.2d 319, 321-22, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989) ("During patent examination the pending claims must be interpreted as broadly as their terms reasonably allow.... The reason is simply that during patent prosecution when claims can be amended, ambiguities should be recognized, scope and breadth of language explored, and clarification imposed.... An essential purpose of patent examination is to fashion claims that are precise, clear, correct, and unambiguous. Only in this way can uncertainties of claim scope be removed, as much as possible, during the administrative process.") (Emboldened added for emphasis).

M.P.E.P. § 2106 (II) continues:

> While it is appropriate to use the specification to determine what applicant intends a term to mean, **a positive limitation from the specification cannot be read into a claim that does not itself impose that limitation**. A broad interpretation of a claim by USPTO personnel will reduce the possibility that the claim, when issued, will be interpreted more broadly than is justified or intended. An applicant can always amend a claim during prosecution to better reflect the intended scope of the claim.
>
> Finally, when evaluating the scope of a claim, every limitation in the claim must be considered. USPTO personnel may not dissect a claimed invention into discrete elements and then evaluate the elements in isolation. Instead, **the claim as a whole must be considered**. See, e.g., *Diamond v. Diehr*, 450 U.S. 175, 188-89, 209 USPQ 1, 9 (1981).

Accordingly, rather than requiring that the claims are insolubly ambiguous, the Board of Patent Appeals and Interferences has stated in a rare precedential opinion that the "USPTO is justified in using a lower threshold showing of ambiguity to support a finding of indefiniteness under 35 U.S.C. § 112, second paragraph, because the applicant has an opportunity and a duty to amend the claims during prosecution to more clearly and precisely define the metes and bounds of the claimed invention and to more

clearly and precisely put the public on notice of the scope of the patent." *Ex parte Miyazaki*, Appeal 2007-3300, November 19, 2008, at p. 12.

With regard to § 112, second paragraph, M.P.E.P. § 2171 states that there are two separate requirements set forth in this paragraph: the claims must set forth the subject matter that applicants regard as their invention; and the claims must particularly point out and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant.

With further regard to the first requirement set forth under § 112, second paragraph, M.P.E.P. § 2171 states the determination of the sufficiency of the claim to satisfy that requirement is subjective because it is dependent on what the applicant for a patent regards as the invention. As that is the case, it is important to note instances in which Applicant's remarks suggest that their invention is something other that which is claimed because such remarks constitute evidence that shows that a claim does not correspond in scope with that which applicant regards as applicant's invention[3]. Furthermore, M.P.E.P. § 2173 states that a clear measure of what an applicant regards as the invention is necessary so that it can be determined whether the claimed invention meets all the criteria for patentability and whether the specification meets the criteria of 35 U.S.C. 112, first paragraph with respect to the claimed invention.

With further regard to the second requirement, M.P.E.P. § 2173 states "[in] reviewing a claim for compliance with 35 U.S.C. 112, second paragraph, the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35 U.S.C. 112, second paragraph, by providing clear warning to others as to what constitutes infringement of the patent".

In this instance, since the claims use of designations such as "CD40', "MAGE" and "gp100" as the sole means of identifying the polypeptides or antigens to which the claims refer, and because the use of laboratory designations only to identify a particular polypeptide or a family of polypeptides renders the claims indefinite because different

[3] See M.P.E.P. § 2172 (II).

laboratories may use the same laboratory designations to define completely distinct polypeptides, it is submitted that the claims fail to delineate the metes and bounds of the subject matter that is regarded as the invention with the requisite clarity and particularity to permit the skilled artisan to know or determine infringing subject matter, so as to satisfy the requirements set forth under 35 U.S.C. § 112, second paragraph.

10. The rejection of claims 1, 3, 5, 11, 12, 15, 16, 18, 19, 21, 22, 29-33, 35, 40, 41, 43, 47, 52, 56, and 57 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is maintained. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Beginning at page 51 of the amendment filed August 11, 2010, Applicant has traversed the propriety of maintaining these grounds of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

This is a "written description" rejection.

As before noted, the considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description'' Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001; hereinafter "Guidelines"). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

These guidelines state that rejection of a claim for lack of written description, where the claim recites the language of an original claim should be rare. Nevertheless, these guidelines further state, "the issue of a lack of written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant has possession of the claimed invention" (*Id.* at 1105). The "Guidelines" continue:

> The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. This problem may arise where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process.

With further regard to the proposition that, as *original* claims, the claims themselves provide *in haec verba* support sufficient to satisfy the written description requirement, the Federal Circuit has explained that *in ipsis verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement:

> Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *See also:* University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

Thus, an original claim may provide written description for itself, but it must still be an adequate written description, *which establishes that the inventor was in possession of the invention*.

In this instance, the claims are directed to a nucleic acid molecule encoding a fusion polypeptide comprising a β2-microglobulin molecule adjoined to a peptide that spans the distance from the C-terminus of the β2-microglobulin molecule to the cell membrane, which in turn is adjoined to a polypeptide that anchors the entire fusion polypeptide to the cell membrane and which consists of the full transmembrane domain and full or partial cytoplasmic domain of a molecule selected from the group consisting of the human CD3 ζ polypeptide, CD40 and the MHC class I heavy chain of HLA-A, HLA-B, or HLA-C.

Since the claimed polynucleotide encodes a fusion polypeptide comprising a β2-microglobulin molecule adjoined via its amino-terminus to an antigenic peptide comprising an MHC class I epitope, wherein the peptide is *derived* from any of a large number of structurally and functionally disparate tumor-associated antigens, it is aptly noted that the claims are directed to a genus that cannot be said to be adequately represented by those peptides that are particularly described by the specification. This is in part because the peptide need only be derived from any of the aforementioned antigens, the structure of the peptide of which the fusion polypeptide encoded by the claimed polynucleotide need not have any particular structure. Given this fact, no one particularly identified peptide (e.g., the peptide of SEQ ID NO: 4, which according to claim 16, e.g., is an antigen derived from AFP, a tumor associated antigen) should be regarded as representative of the genus of antigenic peptides, as a whole, and especially not of the genus that can be so variously used in constructing fusion polypeptides that will be suitably used to achieve the claimed prophylactic or therapeutic effects in treating such a large variety of etiologically and pathogenically diseases. Even if one presumes that the antigenic peptide of which the fusion polypeptide encoded by the claimed polynucleotide is necessarily effective to stimulate an specific immune response against a particular antigen associated with any given disease (i.e., a type of cancer or an infectious disease caused by a certain pathogen), because it has no particular structure, the claims are directed to antigenic peptides that are defined by their immunogenic properties alone; yet, as explained above, a generic statement that defines a genus of substances by *only* their functional activity, i.e., the ability stimulate a specific immune response in a mammal, does not provide an adequate written description of the genus.

To further elaborate upon this issue, Guidelines states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). "Guidelines" further states, "[f]or

inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. Moreover, because the claims encompass a genus of substances having the ability to stimulate immune responses that must be effective to prevent or treat any number of etiologically and pathologically disparate types of cancer or infectious diseases caused by markedly different pathogens, which otherwise may have very different structures, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. In this instance, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; Applicant has not shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; and Applicant has not described distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention at the time the application was filed.

So, in this case, since the claims are so broad, and the disclosure is so comparably limited, it is submitted that any alleged conception has no more specificity than simply a wish to know the identity of any material with that requisite biological properties, which can be used to make the claimed products and then practice the claimed processes, so as to achieve the claimed prophylactic or therapeutic objectives or effects.

In such instances, the alleged conception fails not merely because the field is unpredictable or because of the general uncertainty surrounding experimental sciences, but because the conception is incomplete due to factual uncertainty that undermines the specificity of the inventor's idea of the invention. *Burroughs Wellcome Co. v. Barr Laboratories Inc.*, 40 F.3d 1223, 1229, 32 USPQ2d 1915, 1920 (Fed. Cir. 1994).

Reduction to practice in effect provides the only evidence to corroborate conception (and therefore possession) of the invention.

Then, since the claims are not necessarily limited to known materials (i.e., peptides) having the properties of antigenic peptide of which the fusion protein encoded by the claimed polynucleotide is comprised, but rather to such material that might be identified, given the bid set forth in the instant disclosure to do so, it is noted that one cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483 (Bd. Pat. App. & Int. 1993).

With further regard to the inventions of claims directed to processes that necessarily achieve prophylactic or therapeutic effect, or to products intended for use in achieving such effects, it is noted that any given polypeptide may or may not be *immunogenic* in a mammal, as many polypeptides fail to induce an immune response because the mammal's immune response is *tolerant* to the polypeptide. While this concept is further addressed below, it is noted that Khong et al. (of record), for example, teaches that although two peptides consisting of particular fragments of a particular polypeptide (i.e., TRP2-6b) activate cytotoxic T cells *in vitro*, thereby inducing the cells to release a cytokine (i.e., INF-γ), most of the other peptides consisting of other fragments of the polypeptide, *which were predicted to bind HLA-A2*, only marginally induced such an immune response; see entire document (e.g., page 952, column 1; and page 954, Table VI). This disclosure suggests, despite the ability to predict which peptides are capable of binding MHC class I molecules, the skilled artisan cannot reliably predict which of such peptides are capable of stimulating cytotoxic T cells directed against a tumor associated antigen, such as TRP2-6b or any other antigen associated with a disease.

Furthermore, inasmuch as the claims are directed to a genus of structurally disparate antigenic peptides that are *derived* from tumor associated antigens, it is aptly noted that since their structures may vary substantially many may not elicit an immune response directed against the antigen from which they were originally derived. Then, too, only certain immunogenic fragments might be expected to effectively induce antigen-specific cytotoxic T lymphocytes (CTL) that will kill the cancer cells; other

immunogenic fragments will not be effective. This position is supported, for example, by the teachings of Lu et al. (of record). Lu et al. teaches that four of five immunogenic fragments of the prostate cancer-associated antigen PSMA were capable of inducing antigen-specific CTL killing of target cells, but only one was effective at recognizing prostate tumor cells expressing the protein; see the entire document (e.g., the abstract). Thus, while some immunogenic fragments of any given tumor-associated antigen may effective to stimulate a CTL-mediated response to the immunogenic fragment, it seems that the artisan cannot predict which immunogenic fragments might be used to elicit an effective anti-tumor immune response, which prevents or suppresses the onset, growth, and/or malignant progression of the disease.

As before noted, the Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v. Lederman*, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568).

Furthermore, Applicant is again reminded that "generalized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

In this instance, there is no language that adequately describes with the requisite clarity and particularity the genus of claimed antigenic peptides that can be used to construct the fusion polypeptide encoded by the claimed polynucleotide, which can be used to stimulate an immune response in the subject or patient that will be effective to prevent or treat any given type of cancer or infectious disease, so as to achieve the claimed objective or purpose of using the claimed products or of practicing the claimed processes. Once again, a description of what a material does, rather than of what it is, does not suffice to describe the claimed invention.

This is in part because the Federal Circuit has decided that a generic statement that defines a genus of substances by *only* their functional activity, i.e., the ability exert the requisite anchoring function, does not provide an adequate written description of the

genus. See *The Reagents of the University of California v. Eli Lilly*, 43 USPQ2d 1398 (CAFC 1997). The Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members.

Although *Lilly* related to claims drawn to genetic material, the statute applies to all types of inventions. "Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to the subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods". *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1894 (CAFC 2004). The claimed method depends upon finding the portions of tumor-associated antigens, which can be used to practice the claimed invention to prevent or treat cancer or infectious diseases; without such those portions, which are essential parts of the claimed invention, it is impossible to practice the invention.

In addition, although the skilled artisan could potentially identify peptide fragments of tumor-associated antigens, which are capable of eliciting an anti-tumor immune response, which accordingly may eventually prove suitable for use in treating certain types of cancer, it is duly noted that the written description provision of 35 U.S.C § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*.

> The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*.

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

This position is supported by the numerous references cited in support of the above rejection of the claims under 35 U.S.C. § 112, first paragraph, as failing to satisfy the enablement requirement.

Applicant has argued to the contrary that the written description requirement has been met since, for example, there is declaratory evidence of record showing that certain embodiments of the claimed invention can be used to prevent the formation of tumors in mice immunized before inoculation with tumor cells. In response, it is apparent given the preponderance of evidence now of record that such limited studies should not be considered representative of the results that might be achieved using the claimed invention, which is a polynucleotide encoding a fusion protein comprising a peptide derived from any of large genus of structurally and functionally disparate tumor-associated antigens, to prevent or treat any of large genus of etiologically and pathologically distinct types of cancer or infectious diseases in any animal, including humans, and not just mice.

Thus, although Applicant's arguments have been carefully considered, it is submitted that the instant claims, and the disclosure describing the claimed subject matter, are insufficient to satisfy the written description requirement set forth under 35 U.S.C. § 112, first paragraph.

Double Patenting

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory

obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. The rejection of claims 1, 3, 11, 12, 29-33, 40, and 52 on the ground of nonstatutory obviousness-type double patenting, as being unpatentable over claims 1-16 of U.S. Patent No. 7,319,143-B2, is maintained.

Beginning at page 63 of the amendment filed August 11, 2010, Applicant has traversed the propriety of maintaining these grounds of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

Claims 1-16 of the patent are directed to a DNA molecule encoding a fusion polypeptide comprising a β2-microglobulin molecule adjoined to a peptide, which in turn is adjoined to a fragment of the human CD3 ζ polypeptide comprising its transmembrane and cytoplasmic domains, wherein the β2-microglobulin molecule is also adjoined to another peptide, which is antigenic and related to an autoimmune disease.

Although the claims of the patent are not expressly directed to an antigenic peptide that comprises a MHC class I epitope of any of a tumor-associated antigen, the peptide is antigenic and is related to an autoimmune disease.

It seems that the claimed inventions are substantially similar apart from the fact that the instant claims are directed to an antigenic peptide that is a tumor-associated peptide, whereas the patent's claims are directed to an antigenic peptide related to an autoimmune disease, that it is submitted that the claimed subject matter of the patent renders obvious the claimed subject matter of the instant application.

Applicant has traversed the propriety of maintaining this ground of rejection apparently arguing that the inventions would function differently because of the different properties of antigen-presenting cells and T-cells. In response, it seems that the inventions are not materially or structurally different, but for that difference already noted; and as such contrary to their argument, it would seem that the inventions would not function differently. Even so, most of the claims that are conflicting are drawn to the nucleic acid molecules encoding the fusion polypeptides that are so substantially similar, but for the fact that the peptide is related to different diseases (i.e., a tumor or an autoimmune disease) – and not solely to the cells that are transfected with vectors comprising the claimed nucleic acid molecules.

13. The provisional rejection of claims 1, 3, 5, 11, 12, 15, 16, 18, 19, 21, 22, 29-33, 35, 40, 41, 43, 47, 52, 56, and 57 on the ground of nonstatutory obviousness-type

double patenting, as being unpatentable over claims 1 and 6-25 of copending Application No. 11/541,566, is maintained.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Notably, at page 64 of the amendment filed August 11, 2010, Applicant has requested that this issue be held in abeyance until a notice of allowable subject matter has been given.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 1, 3, 11, 12, 29-32, 40, and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO0101698-A2 (of record).

WO0101698-A2 (Gross et al.) teaches a DNA molecule encoding a chimeric polypeptide comprising a component of a MHC molecule capable of association on a cell surface with an endogenous MHC molecule component of the same class, at a portion of the transmembrane domain and an intracellular region of a signal transduction element capable of activating T cells and, optionally, an antigenic peptide related to an autoimmune disease linked to said chimeric polypeptide by a peptide linker; see entire document (e.g., the abstract). Alternatively, Gross et al. teaches the antigenic peptide of which the fusion protein encoded by the claimed polynucleotide is from a viral antigen (i.e., it is comprised of the Ha 255-262 peptide of influenza virus strain A/Japan/305/57). Gross et al. teaches the MHC component is a monomorphic component, such as the human β2-microglobulin molecule. Gross et al. teaches the human β2-microglobulin molecule is adjoined to the transmembrane and intracellular

(cytoplasmic) regions of a signal transduction element via a bridge peptide. Gross et al. teaches this bridge peptide has a sequence comprised within the membrane-proximal sequence of a class I heavy chain HLA molecule, or more preferably has the sequence that is identical to the instant SEQ ID NO: 1. Gross et al. teaches the chimeric activation receptor of the invention comprises the transmembrane and/or intracellular (cytoplasmic) region of the T-cell receptor CD3, such as the ζ polypeptide. Gross et al. teaches the antigenic peptide is linked to the human β2-microglobulin molecule by a peptide linker. Gross et al. teaches an expression vector comprising the disclosed DNA molecule and cells expressing the fusion polypeptide encoded by the DNA molecule. Gross et al. teaches the vectors are viral vectors.

Although Gross et al. does not expressly teach that the antigenic peptide of which the disclosed fusion protein is comprised may be derived from a tumor associated antigen, absent a showing of any unobvious difference, it is submitted that it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have made the claimed invention comprising an antigenic peptide comprising an MHC class I epitope of a tumor-associated antigen in place of the antigenic peptide derived from an antigen related to an autoimmune disease or a viral protein because Gross et al. teaches the disclosed polynucleotide encoding such a fusion protein is used to elicit a T-cell-mediated immune response against cells expressing the antigen. One of ordinary skill in the art at the time of the invention to have made the claimed invention would have been motivated to do so to determine if the invention could be used to effectively stimulate an anti-tumor immune response in a subject.

Conclusion

16. No claim is allowed.

17. As before noted, the art made of record and not relied upon is considered pertinent to Applicant's disclosure. Lens (*Expert Opin. Biol. Ther.* 2008 Mar; **8** (3): 315-323) reviews the role of vaccine therapy in treating melanoma, disclosing that clinical

responses to melanoma vaccines are still poor and that there currently no melanoma vaccine with a proven efficacy. Morris et al. (*Surg. Oncol. Clin. N. Am.* 2007 Oct; **16** (4): 819-831) reviews the limitations of the cancer vaccines. Prehn (*Cancer Cell Int.* 2005 Aug 1; **5** (1): 25) reviews the reasons that cancer vaccines are ineffective. Bradac et al. (*IDrugs*. 2009 Jul; **12** (7): 435-439) reviews the failure of an HIV vaccine to effectively treat AIDS.

18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Misook Yu can be reached on (571) 272-0839. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Stephen L. Rawlings/
Primary Examiner, Art Unit 1643

slr
October 25, 2010